

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.

**THIS PAGE BLANK (USPTO)**

A7

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 281 309  
A1**

(12)

## EUROPEAN PATENT APPLICATION

(21) Application number: 88301561.2

(51) Int. Cl. 4: **C07D 263/58**, C07D 235/26,  
C07D 413/12, C07D 209/34,  
C07D 417/12, C07D 277/68,  
A61K 31/495

(22) Date of filing: 24.02.88

Claims for the following Contracting States: ES  
+ GR.

(30) Priority: 02.03.87 PCT/US87/00423

(43) Date of publication of application:  
07.09.88 Bulletin 88/36

(84) Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI LU NL SE

(71) Applicant: **PFIZER INC.**  
235 East 42nd Street  
New York, N.Y. 10017(US)

(72) Inventor: **Lowe, John Adams, III**  
28 Coveside Lane  
Stonington Connecticut(US)  
Inventor: **Nagel, Arthur Adam**  
66 Cliffside Drive  
Gales Ferry Connecticut(US)

(74) Representative: **Moore, James William, Dr.**  
Pfizer Limited Ramsgate Road  
Sandwich Kent CT13 9NJ(GB)

(54) Piperazinyl-heterocyclic compounds.

(57) Arylpiperazinyl-ethyl(or butyl)-heterocyclic compounds and their pharmaceutically acceptable acid addition salts are neuroleptic agents. They are useful in the treatment of psychotic disorders.

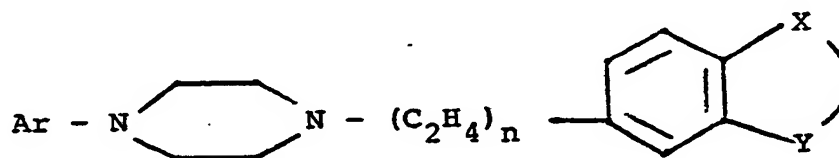
EP 0 281 309 A1

PIPERAZINYL-HETEROCYCLIC COMPOUNDS

The invention relates to arylpiperazinyl-ethyl (or butyl)-heterocyclic compounds and their pharmaceutically acceptable acid addition salts, pharmaceutical compositions containing these compounds, and a method of using them.

Arylpiperazinyl-ethylheterocyclic compounds and their use in the treatment of psychiatric disorders are disclosed in U.S. Patent No. 4,558,060. The aryl group in these prior art compounds is a pyrimidinyl or an optionally substituted phenyl. Compounds with a butyl between the piperazinyl and heterocyclic group are not disclosed, and heterocyclic groups other than benzoxazolones are not disclosed.

The compounds of the invention are of the formula



or the pharmaceutically acceptable acid addition salts thereof wherein Ar is naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; isoquinolyl; 6-hydroxy-8-quinolyl; benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; indanyl optionally substituted by one or two fluoro; 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;  $n$  is 1 or 2; and X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl; benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 3-hydroxyindazolyl; indolyl; spiro[cyclopentane-1,3'-indolyl]; oxindolyl; optionally substituted by one to three of  $(C_1-C_3)$  alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolonyl; benzothiazolonyl; benzoimidazolonyl; or benzotriazolyl.

The optional substitution in the naphthyl and oxindolyl may be in either ring of the naphthyl and oxindolyl group, respectively. Examples of such substitutions are 6-fluoronaphthyl, 4-methoxynaphthyl, 1-ethyloxindolyl and 6-fluorooxindolyl. The optional substitution in the indanyl is in the saturated ring of the indanyl group. Specific substitution of the oxindolyl by  $(C_1-C_3)$  alkyl is by one to three methyl groups, or one ethyl. The optional substitution in the phenyl is for instance at the 3-position.

Preferred compounds are those wherein  $n$  is 1, those wherein X and Y together with the phenyl to which they are attached form benzoxazolonyl, and those wherein Ar is naphthyl or benzoisothiazolyl.

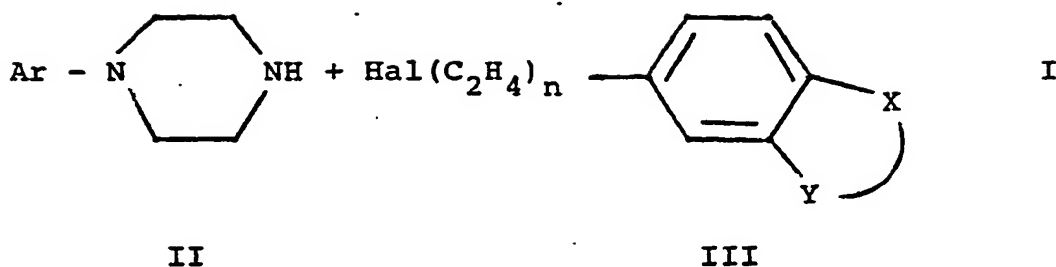
Specific preferred compounds are

- 6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-benzoxazolone
- 6-(2-(4-(8-quinolyl)piperazinyl)ethyl)-benzoxazolone
- 6-(2-(4-(4-quinazolonyl)piperazinyl)ethyl)-benzoxazolone
- 6-(2-(4-(4-phthalazinyl)piperazinyl)ethyl)-benzoxazolone
- 6-(2-(4-(benzoisothiazolyl)piperazinyl)ethyl)-benzoxazolone
- 6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-oxindole, and
- 6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-benzimidazolone.

The present invention also relates to pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. Preferred compositions are those wherein the compound of formula I is a preferred compound or a specific preferred compound as described above.

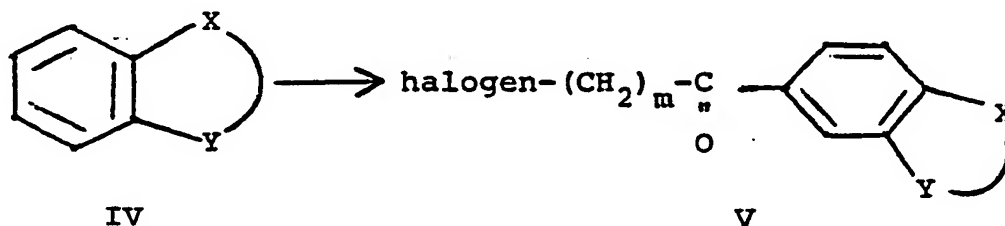
This invention further comprises a method of treating a psychotic disorder by administering to a subject in need of treatment an effective amount of formula I. Preferred methods of treatment are those administering a preferred compound of formula I or a specific preferred compound as described above.

The compounds of formula I may be prepared by reacting piperazines of formula II with compounds of formula III as follows:



wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is generally conducted in a polar solvent such as a lower alcohol, for instance ethanol, dimethylformamide or methylisobutylketone, and in the presence of a weak base such as a tertiary amine base, for instance triethylamine or diisopropylethylamine. Preferably, the reaction is in the further presence of a catalytic amount of sodium iodide, and a neutralizing agent for hydrochloride such as sodium carbonate. The reaction is preferably conducted at the reflux temperature of the solvent used. The piperazine derivatives of formula II may be prepared by methods known in the art. For instance, preparation may be by reacting an arylhalide of the formula ArHal wherein Ar is as defined above and Hal is fluoro, chloro, bromo or iodo, with piperazine in a hydrocarbon solvent such as toluene at about room temperature to reflux temperature for about half an hour to 24 hours. Alternatively, the compounds of formula II may be prepared by heating an amino-substituted aryl compound of the formula ArNH<sub>2</sub> wherein Ar is as defined above with a secondary amine to allow cyclization to form the piperazine ring attached to the aryl group Ar.

The compounds of formula III may be prepared by known methods. For instance, compounds (III) may be prepared by reacting a halo-acetic acid or halo-butyric acid wherein the halogen substituent is fluoro, chloro, bromo or iodo with a compound of the formula IV as follows:



wherein X and Y are as defined above and m is 1 or 3. The compounds (V) are then reduced, e.g. with triethylsilane and trifluoroacetic acid in a nitrogen atmosphere, to form compounds (III).

When Ar is the oxide or dioxide of benzothiazolyl, the corresponding benzothiazolyl is oxidized under acid conditions at low temperatures. The acid used is advantageously a mixture of sulphuric acid and nitric acid.

The pharmaceutically acceptable acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base (I) with about one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration and recrystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic such as methanesulfonic, benzenesulfonic, and related acids.

The neuroleptic activity of the present compounds may be demonstrated by methods based on standard procedures. In one method, adult male Sprague-Dawley rats are pretreated with appropriate doses of the test compound by subcutaneous injection. One half hour later, all rats are injected intraperitoneally with 1 mg/kg apomorphine hydrochloride dissolved in an 0.1% ascorbate solution. The rats are rated behaviorally according to the following scale at 5, 15, 25, 35 and 45 minutes after the apomorphine injection: 0 = alert but not moving, 1 = moving and the cage, 2 = discontinuous sniffing behavior, 3 = continuous sniffing with discontinuous oral movements, and 4 = continuous licking and chewing movements.

The neuroleptic activity of the compounds of this invention makes them useful for treating psychotic disorders in human subjects. For example, these compounds are useful for treating psychotic disorders of the schizophrenic types, and in particular the compounds are useful for removing or ameliorating such symptoms as anxiety, agitation, excessive aggression, tension, and social or emotional withdrawal in

psychotic patients.

A neuroleptic compound of formula I, or a pharmaceutically-acceptable salt thereof, can be administered to a human subject either alone, or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. A compound can be administered orally or parenterally. Parenteral administration includes especially intravenous and intramuscular administration. Additionally, in a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically-acceptable salt thereof, the weight ratio of active ingredient to carrier will normally be in the range from 1:6 to 2:1, and preferably 1:4 to 1:1. However, in any given case, the ratio chosen will depend on such factors as the solubility of the active component, the dosage contemplated and the precise route of administration.

For oral use of a neuroleptic agent of this invention, the compound can be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which can be used include lactose and corn starch, and lubricating agents, such as magnesium stearate, can be added. For oral administration in capsule form, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For intramuscular and intravenous use, sterile solutions of the active ingredient can be prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

When a neuroleptic agent of this invention is to be used in a human subject to treat a psychotic disorder, the daily dosage will normally be determined by the prescribing physician. Moreover, the dosage will vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms. However, in most instances, an effective amount for treating a psychotic disorder will be a daily dosage in the range from 5 to 500 mg, and preferably 50 to 100 mg, in single or divided doses, orally or parenterally. In some instances it may be necessary to use dosages outside these limits.

The following examples are provided solely for the purpose of further illustration.

#### Example 1

##### 6-(2-(4-(1-Naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a 500 ml three-necked round-bottomed flask equipped with mechanical stirrer and N<sub>2</sub> inlet were added 200 g of polyphosphoric acid, 13.51 g (0.1 mole) of benzoxazolone, and 13.89 g (0.1 mole) or bromoacetic acid. The reaction was heated with stirring at 115°C for 2.5 hours and poured into 1 kg ice. The mixture was stirred mechanically for 1 hour to form a purple solid, which was then filtered off and washed with water. The solid was slurried with acetone for 30 minutes, a small amount of purple solid filtered off, and the brown filtrate evaporated. The resulting dark brown gum was slurried with 150 ml ethanol for 30 minutes, and the brown solid filtered off and washed with ethanol. This solid had a m.p. of 192-194°C.

The solid (6.6 g, 0.0257 mole) was placed in a 100 ml three-necked round-bottomed flask equipped with magnetic stirrer, dropping funnel, thermometer, and nitrogen inlet and 19.15 ml (0.257 mole) of trifluoroacetic acid added. Triethylsilane (9.44 ml, 0.0591 mole) was added dropwise to the stirring slurry over 30 minutes. The reaction was stirred overnight at room temperature, then poured into 150 g ice. The mixture was stirred for 15 minutes, and the brown gum filtered off. The gum was dissolved in 100 ml ethyl acetate, and 125 ml cyclohexane added, giving a brown precipitate, which was filtered and washed with cyclohexane. The filtrate was evaporated and the resulting yellow solid slurried with 50 ml isopropyl ether. The pale yellow solid was filtered off and dried to give 2.7 g 6-(2-bromoethyl)-benzoxazolone (11% yield for two steps), m.p. 148-151°C.

B. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and nitrogen inlet were added 0.618 g (2.10 mmol) of N-(1-naphthyl)-piperazine, 0.472 g (1.95 mmol) of 6-(2-bromoethyl)-benzoxazolone, 0.411 ml (2.92 mmol) of triethylamine, 50 ml ethanol, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml methylene chloride, the pH adjusted with aqueous 1N NaOH solution, and a little methanol added to facilitate phase separation. The methylene chloride layer was dried over sodium sulfate and evaporated, then chromatographed on silica gel. Fractions containing the product

were combined and evaporated, the residue taken up in ethyl acetate, treated with hydrochloride gas, and the resulting hydrochloride salt of the product filtered off to give the white solid title compound, m.p. 282-285°C, 213 mg (23% yield).

5

### Example 2

#### 6-(2-(4-(1-Naphthyl)piperazinyl)ethyl)-benzimidazolone

10 A. To a 500 ml three-necked round-bottomed flask equipped with mechanical stirrer and N<sub>2</sub> inlet were added 100 g of polyphosphoric acid, 6.7 g (0.05 mole) of benzoxazolone, and 6.95 g (0.05 mole) of bromoacetic acid. The reaction was heated with stirring at 115°C for 1.5 hours and poured into 1 kg ice. The mixture was stirred mechanically for 1 hour to form a gray solid, which was then filtered off and washed with water. The solid was slurried with acetone for 30 minutes, a small amount of purple solid filtered off, 15 and the brown filtrate evaporated. The resulting dark brown gum was taken up in ethyl acetate/water, and the organic layer washed with water and brine, dried, and evaporated to solid, 6.5 g (51%). NMR (d, DMSO-d<sub>6</sub>): 5.05 (s, 2H), 7.4 (m, 1H), 7.7-8.05 (m, 2H).

The solid (6.0 g, 0.0235 mole) was placed in a 100 ml three-necked round-bottomed flask equipped with magnetic stirrer, dropping funnel, thermometer, and N<sub>2</sub> inlet and 18.2 ml (0.235 mole) of trifluoroacetic acid added. Triethylsilane (8.64 ml, 0.0541 mole) was added dropwise to the stirring slurry over 30 minutes. 20 The reaction was stirred overnight at room temperature, then poured into 150 g ice. The mixture was stirred for 14 minutes, and the pink solid 6-(2-bromoethyl)-benzimidazolone filtered off to give 5.0 g (42% yield for two steps), m.p. 226-230°C.

B. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and N<sub>2</sub> inlet were 25 added 2.64 g (12.4 mmol) of N-(1-naphthyl)-piperazine, 3.0 g (12.4 mmol) of 6-(2-bromoethyl)-benzimidazolone, 1.31 g (12.4 mmol) sodium carbonate, 50 ml methylisobutylketone, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml ethyl acetate, and the ethyl acetate layer washed with brine, dried over sodium sulfate, and evaporated, then chromatographed on silica gel. Fractions containing the 30 product were combined and evaporated, the residue taken up in tetrahydrofuran, treated with HCl gas, and the resulting hydrochloride salt of the product filtered off to give the white solid, m.p. 260-262°C, 716 mg (14% yield).

### 35 Example 3

#### 6-(2-(4-(8-Quinolyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 0.36 g (1.5 mmol) 40 of 6-bromoethyl benzoxazolone, 0.32 g (1.5 mmol) of 8-piperazinyl quinoline, 0.2 g (1.9 mmol) of sodium carbonate, 50 mg of sodium iodide, and 5 ml of ethanol. The reaction was refluxed for 20 hours, cooled, diluted with water, and the pH adjusted to 4 with 1N NaOH, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.3 g of a yellow oil. The oil was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to 45 dryness. The residue was crystallized from isopropanol to give 0.18 g (32%) of a yellow salt, m.p. 200°C. NMR (d, CDCl<sub>3</sub>): 2.74 (m, 2H), 2.89 (m, 6H), 3.44 (m, 4H), 6.76-7.42 (m, 7H), 8.07 (m, 1H), 8.83 (m, 1H).

### Example 4

50

#### 6-(2-(4-(4-Quinazolinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 1.22 g (5.05 mmol) of 6-bromoethylbenzoxazolone, 1.08 g (5.05 mmol) of 4-piperazinylquinoline, 0.85 g (8.0 mmol) of sodium 55 carbonate, 2 mg of sodium iodide, and 35 ml of ethanol. The reaction was refluxed for 3 days, cooled, diluted with water, and the pH adjusted to 4 with 1N HCl. The aqueous layer was separated, the pH adjusted to 7 with 1N NaOH, and the product extracted into ethyl acetate. The ethyl acetate layer was

washed with brine, dried, and evaporated to give 1.3 g of a yellow oil. The oil was crystallized from chloroform (1.1 g), dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness. The residue gave 0.9 g (58%) of a yellow salt, m.p. 200°C. NMR (d, CDCl<sub>3</sub>): 2.72 (m, 6H), 2.86 (m, 2H), 3.83 (m, 4H), 6.9-7.9 (m, 7H), 8.72 (s, 1H).

#### Example 5

##### 6-(2-(4-(4-Phthalazinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 1.13 g (4.7 mmol) of 6-bromoethyl benzoxazolone, 1.0 g (4.7 mmol) of 4-piperazinyl phthalazine, 0.64 g (6.0 mmol) of sodium carbonate, and 30 ml of ethanol. The reaction was refluxed for 20 hours, cooled, diluted with water, and the pH adjusted to 4 with 1N HCl. The aqueous layer was separated, the pH adjusted to 7 with 1N NaOH, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.5 g of a red oil. The oil was chromatographed on silica gel using chloroform/methanol as eluent to give 0.2 g of a pink oil. The oil was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added and the mixture concentrated to give 0.37 g (11%) of a yellow salt, m.p. 200°C. NMR (d, CDCl<sub>3</sub>): 2.78 (m, 2H), 2.88 (m, 6H), 3.65 (m, 4H), 7.0-8.1 (m, 7H), 9.18 (s, 1H).

#### Example 6

##### 6-(2-(4-(4-Methoxy-1-naphthyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 0.24 g (1.0 mmol) of 6-bromoethylbenzoxazolone, 0.24 g (1.0 mmol) of 4-methoxy-1-piperazinyl naphthalene, 0.13 g (1.2 mmol) of sodium carbonate, 25 ml of ethanol. The reaction was refluxed for 36 hours, cooled, diluted with water, and the product extracted into ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.49 g of a yellow oil. The oil was chromatographed on silica gel using chloroform as eluent to give 0.36 g of yellow crystals. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness to give 0.26 g (55%) of white salt crystals, m.p. 200°C. NMR (d, CDCl<sub>3</sub>): 2.8-3.2 (m, 12H), 4.01 (s, 3H), 6.7-7.6 (m, 7H), 8.26 (m, 2H).

#### Example 7

##### 6-(2-(4-(5-Tetralinyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 1.0 g (3.9 mmol) of 6-bromoethylbenzoxazolone, 0.85 g (3.9 mmol) of 5-piperazinyl tetralin, 0.4 g (3.9 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml of isopropanol. The reaction was refluxed for 18 hours, cooled, evaporated to dryness, and the residue dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the precipitate which had formed collected by filtration. The precipitate was suspended in ethyl acetate/water, the pH adjusted to 8.5 with 1N NaOH, and the ethyl acetate layer separated. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.7 g of a solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness to give 0.70 g (40%) of a yellow salt, m.p. > 200°C. NMR (d, CDCl<sub>3</sub>): 1.9 (m, 4H), 2.95 (m, 16H), 6.8-7.2 (m, 6H).

#### Example 8

##### 6-(2-(4-(6-Hydroxy-8-quinolyl)piperazinyl)ethyl)-benzoxazolone

To a 35 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 0.84 g (3.5 mmol) of 6-bromoethylbenzoxazolone, 0.80 g (3.5 mmol) of 6-hydroxy-8-piperazinyl quinoline, 0.37 g (3.5 mmol) of sodium carbonate, 2 mg of sodium iodide, and 30 ml of isopropanol. The reaction was refluxed for 18



hours, cooled, evaporated, and the residue dissolved in ethyl acetate/water. The pH was adjusted to 2.0 with 1N HCl, and the phases separated. The aqueous phase was adjusted to pH 8.5 and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried, and evaporated to give 0.33 g of a yellow solid. The solid was dissolved in ethyl acetate, ethyl acetate saturated with HCl gas added, and the mixture concentrated to dryness. The residue was crystallized from isopropanol to give 0.32 g (20%) of a yellow salt, m.p. > 200°C. NMR (d, CDCl<sub>3</sub>): 2.8 (m, 8H), 3.4 (m, 4H), 6.7-7.3 (m, 7H), 7.7-7.9 (m, 1H).

### Example 9

#### 6-(2-(4-(1-(6-Fluoro)naphthyl)piperazinyl)ethyl)-benzoxazolone

A. To a 1 l round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 345 ml (3.88 mol) of fluorobenzene and 48 g (0.428 mol) of furoic acid. To the stirring suspension was added in portions 120 g (0.899 mol) of aluminum chloride. The reaction was then stirred at 95°C for 16 hours and then quenched by addition to ice/water/1N HCl. After stirring 1 hour, the aqueous layer was decanted off, and benzene and a saturated aqueous solution of sodium bicarbonate added. After stirring 1 hour, the layers were separated, the aqueous layer washed with benzene, acidified, and extracted into ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over sodium sulfate, and evaporated to a solid. The solid was triturated with isopropyl ether to give 5.0 g (6.1%) of white solid 6-fluoro-1-naphthoic acid. NMR (d, DMSO-d<sub>6</sub>): 7.0-8.0 (m, 5H), 8.6 (m, 1H).

B. To a 125 ml round-bottomed flask equipped with condenser, addition funnel, and N<sub>2</sub> inlet were added 5.0 g (26.3 mmol) of 6-fluoro-1-naphthoic acid and 50 ml acetone. To the stirring suspension were added dropwise 6.25 ml (28.9 mmol) of diphenyl phosphoryl azide and 4 ml (28.9 mmol) of triethylamine. The reaction was refluxed 1 hour, poured into water/ethyl acetate, and filtered. The filtrate was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was further treated with HCl to form the hydrochloride salt and then liberated with sodium hydroxide to afford the free base 6-fluoro-1-amino-naphthalene as an oil, 1.0 g (24%).

C. To a 125 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 1.0 g (6.21 mmol) of 6-fluoro-1-amino naphthalene, 1.8 g (7.76 mmol) of N-benzyl bis(20chloroethyl)amine hydrochloride, 3.3 ml (19.2 mmol) of diisopropylethylamine, and 50 ml isopropanol. The reaction was refluxed 24 hours, cooled, and evaporated to an oil. The oil was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using methylene chloride as eluent to afford 1.5 g (75.5%) of an oil, 1-benzyl-4-(6-fluoronaphthyl)-piperazine.

D. To a 125 ml round-bottomed flask equipped with N<sub>2</sub> inlet were added 1.5 g (4.69 mmol) of 1-benzyl-4-(6-fluoronaphthyl)-piperazine, 1.2 ml (31.3 mmol) of formic acid, 3.0 g 5% palladium on carbon, and 50 ml ethanol. The reaction was stirred at room temperature for 16 hours, the catalyst filtered under N<sub>2</sub>, and the solvent evaporated. The oil, N-(1-(6-fluoro)naphthyl)-piperazine (0.420 g, 39%), was used directly in the following step.

E. To a 100 ml round-bottomed flask equipped with magnetic stirrer, condenser, and N<sub>2</sub> inlet were added 0.420 g (1.83 mmol) of N-(1-naphthyl)piperazine, 0.440 g (1.83 mmol) of 6-(2-bromoethyl)-benzoxazolone, 194 mg (1.83 mmol) of sodium carbonate, 50 ml methylisobutylketone, and a catalytic amount of sodium iodide. The reaction was refluxed for 3 days, cooled, and evaporated to a brown gum. The gum was partitioned between 50 ml water and 75 ml ethyl acetate, the pH adjusted with aqueous 1N NaOH solution, the layers separated, and the ethyl acetate layer washed with water and brine. The ethyl acetate layer was dried over sodium sulfate and evaporated, then chromatographed on silica gel. Fractions containing the product were combined and evaporated, the residue taken up in either/methylene chloride, treated with HCl gas, and the resulting hydrochloride salt of the product filtered off to give a white solid, m.p. 295-300°C, 214 mg (22% yield).

### Example 10

#### 6-(4-(4-(1-Naphthyl)piperazinyl)butyl)-benzoxazolone

A. To a 500 ml round-bottomed flask equipped with mechanical stirrer and N<sub>2</sub> inlet were added 200 g polyphosphoric acid, 16.7 g (0.1 mol) 4-bromobutyric acid, and 13.51 g (0.1 mol) benzoxazolone. The reaction was heated at 115°C for 1 hour and 60°C for 1.5 hours. It was then poured onto ice, stirred for 45

minutes and the solid filtered and washed with water. The solid was suspended in acetone, stirred for 20 minutes, filtered, washed with petroleum ether, and dried to give 12.3 g (43%) of white solid 6-(4-bromobutyryl)-benzoxazolone. NMR (d, DMSO- $d_6$ ): 1.77 (quin, 2H), 3.00 (t, 2H), 3.45 (t, 2H), 7.0-7.8 (M, 3H).

B. To a 100 ml three-necked round-bottomed flask equipped with dropping funnel, thermometer, and  $N_2$  inlet were added 10 g (0.035 mol) 6-(4-bromobutyryl)-benzoxazolone and 26.08 ml (0.35 mol) trifluoroacetic acid. To the stirring suspension was added dropwise 12.93 ml (0.080 mol) triethylsilane, and the reaction stirred at room temperature for 16 hours. The reaction was then poured into water, and the resulting white solid filtered and washed with water. It was then suspended in isopropyl ether, stirred, and filtered to afford white solid 6-(4-trifluoroacetoxybutyl)-benzoxazolone, m.p. 100-103°C, 10.47 g (98.7%).

C. To a 250 ml round-bottomed flask equipped with  $N_2$  inlet were added 5.0 g (0.0164 mol) 6-(trifluoroacetoxybutyl)-benzoxazolone, 100 ml methanol, and 1 g sodium carbonate. The reaction was stirred at room temperature for 1 hour, evaporated, and the residue taken up in methylene chloride/methanol, washed with aqueous HCl, dried over sodium sulfate, and evaporated to white solid 6-(4-hydroxybutyl)-benzoxazolone, m.p. 130-133°C, 2.57 g (75.7%).

D. To a 100 ml round-bottomed flask equipped with condenser and  $N_2$  inlet were added 2.2 g (0.0106 mol) 6-(4-hydroxybutyl)-benzoxazolone, 2.12 g (0.00808 mol) triphenylphosphine, and 200 ml carbon tetrachloride. The reaction was refluxed for 3 days, evaporated, and chromatographed on silica gel using methylene chloride/ethyl acetate as eluent to afford 1.8 g (75.3 %) of white solid 6-(4-chlorobutyl)-benzoxazolone, m.p. 125-127°C.

E. To a 125 ml round-bottom flask equipped with condenser and  $N_2$  inlet were added 0.658 g (3.10 mmol) of 6-(4-chlorobutyl)-benzoxazolone, 0.7 g (3.10 mmol) of N-(1-naphthyl)piperazine, 0.328 g sodium carbonate, 2 mg sodium iodide, and 50 ml isopropanol. The reaction was refluxed for 3 days, evaporated, taken up in methylene chloride, washed with water; dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate as eluent, and the product dissolved in acetone, precipitated with ethereal HCl, and the white solid filtered, washed with acetone, and dried to afford 0.676 g (46.0%) of a white solid, m.p. 231-233°C.

#### Example 11

##### 6-(2-(4-(3-(N-(3-Trifluoromethyl)phenyl)indazolyl)-piperazinyl)ethyl)benzoxazolone

To a 125 ml round-bottomed flask equipped with condenser were added 1.0 g (2.89 mmol) of N-(3-trifluoromethylphenyl)indazolyl)piperazine, 0.70 g (2.89 mmol) of 6-(2-bromoethyl)benzoxazolone, 0.31 g (2.89 mmol) of sodium carbonate, and 50 ml of methyl isobutyl ketone, and the mixture refluxed 18 hours. The reaction was cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was isolated, washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using ethyl acetate/methylene chloride as eluent, and the product fractions collected and dissolved in ether, precipitated with hydrochloride gas, and the solid collected to give the hydrochloride salt of the title compound, m.p. 280-282°C, 0.75 g (47%).

#### Example 12

##### 5-(2-(4-(1-Naphthyl)piperazinyl)ethyl)oxindole

A. To a 250 ml round-bottomed flask equipped with condenser and  $N_2$  inlet were added 30.7 g (230 mmol) aluminum chloride, 150 ml carbon disulfide, and 3.8 ml (48 mmol) chloroacetyl chloride. To the stirring mixture was added 5.0 g (37 mmol) of oxindole portionwise over 15 minutes. The reaction was stirred a further 10 minutes, then refluxed 2 hours. The reaction was cooled, added to ice, stirred thoroughly, and the beige precipitate filtered, washed with water, and dried to afford 7.67 g (97%) of 5-chloroacetyloxindole. NMR (d, DMSO- $d_6$ ): 3.40 (s, 2H), 5.05 (s, 2H), 6.8-7.9 (m, 3H).

B. To a 100 ml round-bottomed flask equipped with condenser and  $N_2$  inlet were added 5.0 g (23.9 mmol) of 5-chloroacetyl oxindole and 18.5 ml trifluoroacetic acid. To the stirring solution was added 8.77 ml (54.9 mmol) of triethylsilane while cooling to prevent exotherm, and the reaction stirred 16 hours at room temperature. The reaction was then poured into ice water, stirred, and the beige solid filtered, washed with water and hexane, and dried to give 5-(2-chloroethyl)oxindole, m.p. 168-170°C., 3.0 g (64%).

C. To a 50 ml round bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 370 mg (1.69 mmol) 5-(2-chloroethyl)oxindole, 400 mg (1.69 mmol) N-(1-naphthyl)piperazine hydrochloride, 200 mg (1.69 mmol) sodium carbonate, 2 mg sodium iodide, and 50 ml methylisobutylketone. The reaction was refluxed 24 hours, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel with ethyl acetate, and the product fractions collected and evaporated to give a foam. The foam was dissolved in ether, treated with HCl gas, and the precipitate collected, washed with ether, and dried to afford a white solid, m.p. 303-305°C, 603 mg (84%).

10

Example 136-(2-(4-(4-(2,1,3-Benzothiadiazolyl)piperazinyl)ethyl)-benzoxazolone

15 A. To a 125 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 2.0 g (13.2 mmol) 4-amino-2,1,3-benzothiadiazole, 2.54 g (13.2 mmol) mechlorethamine hydrochloride, 4.19 g (39.6 mmol) sodium carbonate, 2 mg sodium iodide, and 50 ml ethanol. The reaction was refluxed 2 days, cooled, and evaporated. The residue was taken up in methylene chloride, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/methanol as eluent, and the product fractions collected and evaporated to an oil of 4-(2,1,3-benzothiadiazolyl)-N-methylpiperazine, 628 mg (20%). NMR (d, CDCl<sub>3</sub>): 2.5 (s, 3H), 2.8 (m, 4H), 3.6 (m, 4H), 6.8 (m, 1H), 7.5 (m, 2H).

20 B. To a 25 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 620 mg (2.64 mmol) of 4-(2,1,3-benzothiadiazolyl)-N-methylpiperazine, 0.224 ml (2.64 mmol) vinyl chloroformate, and 15 ml dichloroethane. The reaction was refluxed 16 hours, cooled, and evaporated. The residue was chromatographed on silica gel using methylene chloride/ethyl acetate as eluent, and the product fractions collected to give yellow solid 4-(2,1,3-benzothiadiazolyl)-N-vinyloxycarbonylpiperazine, 530 mg (69%). NMR (d, CDCl<sub>3</sub>): 3.6 (m, 4H), 3.8 (m, 4H), 4.4-5.0 (m, 2H), 6.6-7.8 (m, 4H).

30 C. To a 50 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 530 mg (1.83 mmol) 4-(2,1,3-benzothiadiazolyl)-N-vinyloxycarbonylpiperazine and 25 ml ethanol, and the suspension saturated with HCl gas. The reaction was refluxed 2.75 hours, cooled, and evaporated. The residue was triturated with acetone to give a yellow solid N-(2,1,3-benzothiadiazolyl)-piperazine, m.p. 240-244°C., 365 mg (62%).

35 D. To a 125 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 365 mg (1.13 mmol) N-(2,1,3-benzothiadiazolyl)-piperazine, 275 mg (1.13 mmol) 6-(2-bromoethyl)benzoxazolone, 359 mg (3.39 mmol) sodium carbonate, 2 mg sodium iodide, and 40 ml ethanol. The reaction was heated at reflux for 2 days, cooled, and evaporated. The residue was taken up in methylene chloride, washed with water, dried over sodium sulfate, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/methanol as eluent and the product fractions collected, dissolved in methylene chloride/methanol, precipitated by addition of an ethereal solution of HCl, and the solid filtered, washed with ether, and dried to give 228 mg (45%), m.p. 166-170°C.

Example 14

45

6-(2-(4-(1-Naphthyl)-piperazinyl)ethyl)benzothiazolone

To a 100 ml round-bottomed flask equipped with condenser and N<sub>2</sub> inlet were added 1.0 g (3.88 mmol) of 6-(2-bromoethyl)benzothiazolone, 822 mg (3.88 mmol) N-(1-naphthyl)piperazine, 410 mg (3.88 mmol) sodium carbonate, and 50 ml methylisobutylketone. The reaction was refluxed for 24 hours, cooled, and evaporated. The residue was taken up in ethyl acetate, washed with water and brine, dried over sodium sulfate, and evaporated. The resulting solid was treated with hot ethyl acetate to afford a white solid, m.p. 198-220°C, 540 mg (36%).

55

Example 15

6-(2-(4-(3-Benzisothiazolyl)piperazinyl)ethyl)benzoxazolone

To a 125 ml round-bottomed flask equipped with condenser were added 4.82 g (0.022 mol) of N-(3-benzisothiazolyl)piperazine (prepared according to the procedure given in U.S. Patent 4,411,901), 5.32 g (0.022 mol) of 6-(2-bromo)ethylbenzoxazolone, 2.33 g (0.022 mol) of sodium carbonate, and 50 ml of methyl isobutyl ketone. The mixture was refluxed for 18 hours. The reaction was cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was isolated, washed with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to an oil. The oil was chromatographed on silica gel using ethyl acetate as eluent, and the product fractions collected and triturated with methylene chloride/isopropyl ether to give a white solid, m.p. 185-187°C. NMR (CDCl<sub>3</sub>): 1.7 (bs,1H), 2.8 (m,8H), 3.6 (m,4H), 6.9-8.0 (m,7H).

Example 165-(2-(4-(1,2-Benzisothiazol-3-yl)piperazinyl)ethyl)-oxindole

To a 125 ml round-bottomed flask equipped with N<sub>2</sub> inlet and condenser were added 0.62 g (3.20 mmol) 5-(2-chloroethyl)-oxindole, 0.70 g (3.20 mmol) N-(1,2-benzisothiazol-3-yl)piperazine, 0.68 g (6.40 mmol) sodium carbonate, 2 mg sodium iodide, and 30 ml methylisobutyl ketone. The reaction was refluxed 40 hours, cooled, filtered, and evaporated. The residue was chromatographed on silica gel, eluting the byproducts with ethyl acetate (1 l) and the product with 4% methanol in ethyl acetate (1.5 l). The product fractions (R<sub>f</sub> = 0.2 in 5% methanol in ethyl acetate) were evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid was filtered and washed with ether, dried, and washed with acetone. The latter was done by slurrying the solid with acetone and filtering. The title compound was obtained as a high melting, non-hygroscopic solid product, m.p. 288-288.5°C, 0.78 g (59%).

In a manner analogous to that for preparing 5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-oxindole, the following compounds were made:

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-ethyloxindole hydrochloride, 25%, m.p. 278-279°C;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-methyloxindole hydrochloride hemihydrate, 42%, m.p. 283-285°C; MS(%) : 392(1), 232(100), 177(31); Anal. for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>OS.HCl.1/2H<sub>2</sub>O: C 60.33, H 5.98, N 12.79. Found: C 60.37, H 5.84, N 12.77;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1-(3-chlorophenyl)oxindole hydrochloride hydrate, 8%, m.p. 221-223°C; MS(%) : 488(1), 256(4), 232(100), 177(15); Anal. for C<sub>27</sub>H<sub>25</sub>ClN<sub>4</sub>OS.HCl.H<sub>2</sub>O: C 59.67, H 5.19, N 10.31. Found: C 59.95, H 5.01, N 10.14;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-3,3-dimethyloxindole hydrochloride hemihydrate, 40%, m.p. 289-291°C; MS(%) : 406(1), 232(100), 177(42); Anal. for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>OS.HCl.1/2H<sub>2</sub>O: C 61.11, H 6.24, N 12.39. Found: C 61.44, H 6.22, N 12.01;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1,3-dimethyloxindole, 76%, m.p. 256°C;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-spiro[cyclopentane-1,3'-indoline]-2'-one hydrochloride hemihydrate, 50%, m.p. 291-293°C (dec.); MS(%) : 432(1), 232(100), 200(11), 177(36); Anal. for C<sub>25</sub>H<sub>28</sub>N<sub>4</sub>OS.HCl.1/2H<sub>2</sub>O: C 62.81, H 6.33, N 11.72. Found: C 63.01, H 6.32, N 11.34;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-1,3,3-trimethyloxindole hydrochloride hemihydrate, 63%, m.p. 225-257°C; MS(%) : 420(1), 232(100), 177(37); Anal. for C<sub>24</sub>H<sub>28</sub>N<sub>4</sub>OS.HCl.1/2H<sub>2</sub>O: C 61.85, H 6.49, N 12.02. Found: C 61.97, H 6.34, N 11.93;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-fluorooxindole hydrochloride hydrate, 18%, m.p. 291-293°C; MS(%) : 396(1), 232(100), 177(53); Anal. for C<sub>21</sub>H<sub>21</sub>F<sub>2</sub>OS.HCl.1/2H<sub>2</sub>O: C 55.93, H 5.36, N 12.42. Found: C 56.39, H 5.30, N 12.19.

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-7-fluorooxindole hydrochloride, 9%, m.p. 253°C;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-chlorooxindole hydrochloride, 20%, m.p. > 300°C; MS(%) : 488(1), 256(4), 232(100), 177(15); Analysis for C<sub>21</sub>H<sub>21</sub>ClN<sub>4</sub>OS.HCl.1/2H<sub>2</sub>O: C 52.50, H 4.71, N 11.39. Found: C 52.83, H 4.93, N 11.42;

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-fluoro-3,3-dimethyloxindole hydrochloride, 35%, m.p. 284-286°C; Anal. for C<sub>23</sub>H<sub>26</sub>FN<sub>4</sub>OS.HCl.H<sub>2</sub>O: C 57.67, H 5.89, N 11.70. Found: C 58.03, H 5.79, N 11.77.

5-(4-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)oxindole hemihydrate, 26%, m.p. 131-135°C; MS(%) : 406(2), 270(8), 243(65), 232(23), 177(45), 163(100); Anal. for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>OS.1/2H<sub>2</sub>O: C 66.48, H 6.55, N 13.48. Found: C 66.83, H 6.30, N 13.08;

5-(4-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)-7-fluorooxindole hydrate, 7%, m.p. 126-129°C; MS(%) :

424(3); Anal. for  $C_{22}H_{25}FN_4OS \cdot H_2O$ : C 57.67, H 5.89, N 11.70. Found: C 57.96, H 5.62, N 11.47;

5-(4-(4-(1,2-benzisothiazol-3-yl)piperazinyl)butyl)-1-ethyloxindole hemihydrate, 25%, m.p. 126-128°C; MS(%): 434(2), 298(10), 271(55), 232(34), 177(53), 163(100); Anal. for  $C_{25}H_{28}N_4OS \cdot 1/2 H_2O$ : C 67.69, H 7.04, N 12.63. Found: C 67.94, H 6.73, N 12.21;

5 5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-1-ethyloxindole hydrochloride hydrate, 21%, m.p. >300°C; MS(%): 399(1), 225(96), 182(30), 70(100); Anal. for  $C_{24}H_{24}N_4O \cdot HCl \cdot H_2O$ : C 68.78, H 7.10, N 9.26. Found: C 69.09, H 6.72, N 9.20;

5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-6-fluorooxindole hydrochloride, 23%, m.p. 289-291°C; MS(%): 389(1), 232(3), 225(100), 182(32), 70(84); Anal. for  $C_{24}H_{24}FN_4O \cdot HCl \cdot 1/2 CH_2Cl_2$ : C 62.82, H 5.60, N 8.97. Found: C 62.42, H 5.82, N 8.77; and

10 5-(2-(4-(naphthalen-1-yl)piperazinyl)ethyl)-7-fluorooxindole hydrochloride, 22%, m.p. 308°C (dec.); MS(%): 389(1), 225(100); Anal. for  $C_{24}H_{24}FN_4O \cdot HCl \cdot CH_2Cl_2$ : C 58.78, H 5.93, N 8.23. Found: C 58.82, H 5.80, N 8.27

15

### Example 17

#### 6-(4-(2-(3-Benzisothiazolyl)piperazinyl)ethyl)phenyl)benzothiazolone

20 To a 100 ml round-bottomed flask equipped with condenser and  $N_2$  inlet were added 1.03 g (4 mmol) 6-(2-bromoethyl)-benzothiazolone, 0.88 g (4 mmol) N-benzisothiazolylpiperazine, 0.84 g (8 mmol) sodium carbonate, 2 mg sodium iodide, and 40 ml methylisobutyl ketone. The reaction was refluxed 36 hours, cooled, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel using ethyl acetate as eluent to afford an oil, which was taken up in methylene chloride and precipitated by addition of  
25 ether saturated with HCl. The solid was filtered, washed with ether, dried briefly, washed with a minimal amount of acetone and dried to afford a white solid, m.p. 288-290°C, 1.44 g (78.7%).

### Example A

30

A. Following the general procedure for the preparation of 5-(chloroacetyl)oxindole in Example 12A, the following intermediates were prepared from the appropriate oxindoles:

5-(chloroacetyl)-1-ethyl-oxindole (81%, m.p. 157-159°C, NMR( $CDCl_3$ ): 1.30(t,3H), 3.60(s,2H), 3.85(q,2H), 4.70(s,2H), 6.85-8.15(m,2H);

35 5-(chloroacetyl)-1-methyloxindole ( $C_{11}H_{10}ClNO_2$ , 92%, m.p. 201-202°C;

1-(3-chlorophenyl)-5-(chloroacetyl)oxindole, 98%, m.p. 143-145°C, NMR(DMSO- $d_6$ ): 3.85(br s,2H), 5.10(s,2H), 6.8(d,1H), 7.4-7.6(m,4H), 7.9(s + d,2H); MS(%): 319(17), 270(100), 179(46), 178(38);

1,3-dimethyl-5-(chloroacetyl)oxindole, 97%, m.p. 206-207°C;

5'-(chloroacetyl)-spirocyclopentane[1,3']-indol-2'one, 99%, m.p. 203-204°C(dec.); NMR(DMSO- $d_6$ ): 2.0(br s,8H), 4.95(s,2H), 6.9(d,1H), 7.8(d + s,2H), 10.6(br s,1H);

40 5-(chloroacetyl)-1,3,3-trimethyloxindole, 82%, m.p. 182-185°C, NMR( $CDCl_3$ ): 1.45(s,6H), 3.25(s,3H), 4.65(s,2H), 6.9(d,1H), 7.9(s,1H), 8.0(d,1H);

6-fluoro-5-(chloroacetyl)oxindole, 96%, m.p. 178-180°C; NMR(DMSO- $d_6$ ): 3.5(s,2H), 4.8(d,2H), 6.7-7.2(m,2H), 7.8(d,1H);

45 7-fluoro-5-(chloroacetyl)oxindole, 91%, m.p. 194-196°C, NMR(DMSO- $d_6$ ): 3.68(s,2H), 5.13(s,2H), 7.65-7.9(dd,2H);

6-chloro-5-(chloroacetyl)oxindole, 99%, m.p. 206-207°C;

5-(chloroacetyl)-3,3-dimethyl-6-fluorooxindole, 89%, m.p. 185-188°C;

5-( $\gamma$ -chlorobutyryl)oxindole, 84%, oil, MS(%): 239, 237(55);

50 1-ethyl-5-( $\gamma$ -chlorobutyryl)oxindole, 99%, oil, NMR( $CDCl_3$ ): 1.2(t,3H), 1.5-2.7(m,5H), 3.0-3.2(m,2H), 3.5-4.0(m,3H), 6.8-7.0(d,1H), 7.9(s,1H), 7.95(d,1H), and

5-( $\gamma$ -chlorobutyryl)-7-fluorooxindole, 53%, m.p. 156-160°C.

55

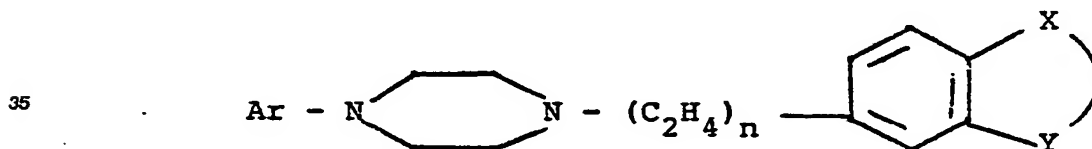
**Example B**

By the same procedure as that used to prepare 5-(2-chloroethyl)oxindole in Example 12B, the following were prepared:

- 5 5-(2-chloroethyl)-1-ethyloxindole, 93%, m.p.120-122°C; NMR(CDCl<sub>3</sub>): 1.30(t,3H), 3.1(t,2H), 3.55(s,2H), 3.65-4.0(m,4H), 6.8-7.3(m,3H);
- 5-(2-chloroethyl)-1-methyloxindole, 99%, m.p.127-130°C; NMR(CDCl<sub>3</sub>): 3.1(t,2H), 3.2(s,2H), 3.5(s,2H), 3.75(t,2H), 6.8(d,1H), 7.15(s,1H), 7.2(d,1H);
- 5-(2-chloroethyl)-1-(3-chlorophenyl)oxindole, 83%, m.p. 75-76°C;
- 10 5-(2-chloroethyl)-1,3-dimethyloxindole, 58%, m.p.73-75°C, NMR(CDCl<sub>3</sub>): 1.45-1.55(d,3H), 3.0-3.2(t,2H), 3.25(s,3H), 3.30-3.60(q,1H), 3.65-3.90(t,2H), 6.85-6.90(d,1H), 7.15(s,1H), 7.15-7.30(d,1H);
- 5'-(2-chloroethyl)-spiro[cyclopentane-1,3'-indoline]-2'-one, 92%, m.p.140-142°C; NMR(DMSO-d<sub>6</sub>): 2.8(br s,8H), 2.90(t,2H), 3.7(t,2H), 6.6-7.1(m,3H), 10.2(br s,1H);
- 5-(2-chloroethyl)-1,3,3-trimethyloxindole, 83%, oil;
- 15 5-(2-chloroethyl)-6-fluorooxindole, 62%, m.p.188-190°C; NMR(DMSO-d<sub>6</sub>) 3.05(t,2H), 3.5(2,2H), 3.85(t,2H), 6.6-7.3(m,2H);
- 5-(2-chloroethyl)-7-fluorooxindole, 79%, m.p.176-179°C; MS(%); 213(50), 180(20), 164(100), 136(76);
- 5-(2-chloroethyl)-6-chlorooxindole, 94%, m.p.210-211°C;
- 5-(2-chloroethyl)-3,3-dimethyl-6-fluorooxindole (C<sub>12</sub>H<sub>13</sub>ClFNO, 84%, m.p.195-198°C, NMR(DMSO-d<sub>6</sub>): 1.3-
- 20 (s,6H), 3.05(t,2H), 3.7(t,2H), 6.65(d,1H), 7.1(d,1H), 10.1(br s,1H);
- 5-(4-chlorobutyl)oxindole, 40%, oil, NMR(CDCl<sub>3</sub>): 1.6-2.0(m,4H), 2.6(m,2H), 3.6(m,4H), 6.8-7.15(m,3H), 9.05(br s,1H);
- 5-(4-chlorobutyl)-1-ethyloxindole, 48%, oil, NMR(CDCl<sub>3</sub>): 1.25(t,3H), 1.5-1.95(m,4H), 2.6(m,2H), 3.5(s,2H), 3.55(t,2H), 3.75(q,2H), 6.7-7.2(m,3H); and
- 25 5-(4-chlorobutyl)-7-fluorooxindole, 71%, m.p.168-173°C.

**Claims**

- 30 1. A compound of the formula



or a pharmaceutically acceptable acid addition salt thereof, wherein

- 40 Ar is naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; 6-hydroxy-8-quinolyl; isoquinolyl; quinazolyl; benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; Indanyl optionally substituted by one or two fluoro; 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;
- 45 n is 1 or 2; and

- X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl; benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-hydroxyindazolyl; indolyl; spiro[cyclopentane-1,3'-indolyl]; oxindolyl optionally substituted by one to three of (C<sub>1</sub>-C<sub>3</sub>)alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolonyl; benzothiazolonyl; benzimidazolonyl; or benzotriazolyl.
- 50

2. A compound according to claim 1, characterized in that X and Y together with the phenyl to which they are attached form benzoxazolonyl or oxindole.

3. A compound according to claim 1 or 2, characterized in that Ar is naphthyl and n is 1.

4. A compound according to claim 1 or 2, characterized in that Ar is benzoisothiazolyl and n is 1.

- 55 5. A compound according to claim 1 wherein said compound is:-

6-(2-(4-(4-phthalazinyl)piperazinyl)ethyl)-benzoxazolone  
6-(2-(4-(benzoisothiazolyl)piperazinyl)ethyl)-benzoxazolone  
6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-oxindole, and

6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-benzimidazolone

6-(2-(4-(1-naphthyl)piperazinyl)ethyl)-benzoxazolone

6-(2-(4-(8-quinolyl)piperazinyl)ethyl)-benzoxazolone

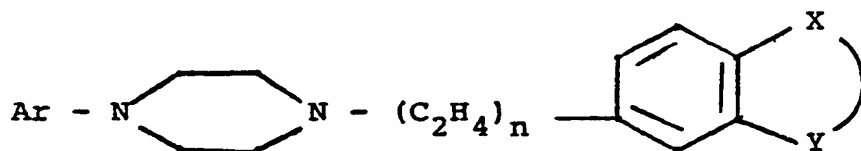
6-(2-(4-(4-quinazoliny)piperazinyl)ethyl)-benzoxazolone

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5, and a pharmaceutically acceptable carrier.

7. A compound according to claim 1 for use in medicine particularly for the treatment of psychotic disorder.

10 Claims for the following contracting States: ES, GR

1. A process for preparing a compound of the formula



20 or a pharmaceutically acceptable acid addition salt thereof, wherein

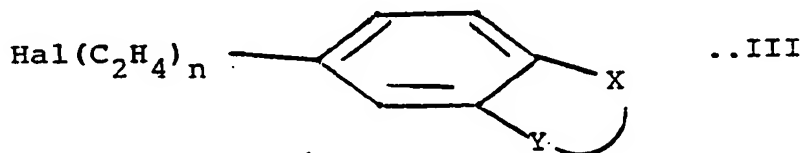
Ar is naphthyl optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano or nitro; quinolyl; 6-hydroxy-8-quinolyl; isoquinolyl; quinazolyl; benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro; benzothiazolyl; benzothiadiazolyl; benzotriazolyl; benzoxazolyl; benzoxazolonyl; indolyl; indanyl optionally substituted by one or two fluoro; 3-indazolyl optionally substituted by 1-trifluoromethylphenyl; or phthalazinyl;

n is 1 or 2; and

X and Y together with the phenyl to which they are attached form quinolyl; 2-hydroxyquinolyl; benzothiazolyl; 2-aminobenzothiazolyl; benzoisothiazolyl; indazolyl; 2-hydroxyindazolyl; indolyl; spiro[cyclopentane-1,3'-indolyl]; oxindolyl optionally substituted by one to three of (C<sub>1</sub>-C<sub>3</sub>)alkyl, or one of chloro, fluoro or phenyl, said phenyl optionally substituted by one chloro or fluoro; benzoxazolyl; 2-aminobenzoxazolyl; benzoxazolonyl; 2-aminobenzoxazolonyl; benzothiazolonyl; benzoimidazolonyl; or benzotriazolyl characterized by reacting piperazines of the formula



40 wherein Ar is as defined above, with a compound of the formula



wherein X and Y are as defined above and Hal is fluoro, chloro, bromo or iodo.

2. A process according to claim 1, characterized in that X and Y together with the phenyl to which they are attached form benzoxazolonyl or oxindole.

3. A process according to claim 1 or 2, characterized in that Ar is naphthyl and n is 1.

4. A process according to claim 1 or 2, characterized in that Ar is benzoisothiazolyl and n is 1.



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 88 30 1561

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	EP-A-0 110 781 (RIOM LABORATOIRES C.E.R.M.) * Claims 1-3,10,11 *	1,6,7	C 07 D 263/58 C 07 D 235/26 C 07 D 413/12 C 07 D 209/34 C 07 D 417/12 C 07 D 277/68 A 61 K 31/495
A	GB-A-2 177 395 (SANDOZ LTD) * Claims *	1,6,7	
A	US-A-4 179 505 (A.H.M. RAEYMAEKERS) * Claims 1,14-39 *	1,6	
A	EP-A-0 196 096 (SUMITOMO) * Claims 1,5,9,10 *	1,6,7	
A	EP-A-0 174 811 (SMITHKLINE BECKMAN CORP.) * Claims 1,3 *	1,6,7	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 263/00 C 07 D 235/00 C 07 D 413/00 C 07 D 209/00 C 07 D 417/00 C 07 D 277/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 07-06-1988	Examiner HENRY J.C.
<b>CATEGORY OF CITED DOCUMENTS</b>			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

EPO FORM 1503 03.82 (P0401)